1,025,041

PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl.:—C 07 c, d // A 61 k

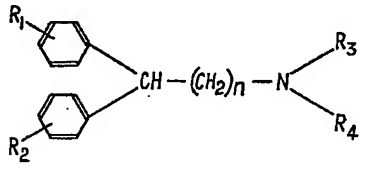
COMPLETE SPECIFICATION

Process for the manufacture of Diphenylalkylamines

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a body corporate recognised under German Law, of 6230 Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

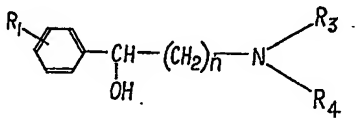
The present invention relates to a process for the manufacture of diphenylalkylamines which have a beneficial physiological effect, especially on the heart and on blood circulation. The invention also relates to processes for the manufacture of pharmaceutical preparations, having cardiac and circulatory action containing diphenylalkylamines or their physiologically tolerable salts as the active ingredients.

The present invention provides diphenylalkylamines of the formula



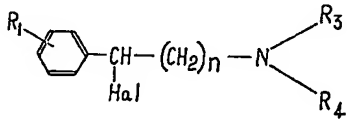
(I)

in which R_1 and R_2, which may be identical or different, represent hydrogen, an alkyl group having 1—3 carbon atoms, an alkoxy group having 1—3 carbon atoms, or halogen, especially chlorine, R_3 represents hydrogen or an alkyl group having 1—3 carbon atoms, and R_4 represents hydrogen, an alkyl group having 1—4 carbon atoms, an aralkyl group having up to 4 carbon atoms in the alkylene chain which may be substituted in the phenyl nucleus by alkyl or alkoxy groups each having 1—3 carbon atoms, or in which R_3 and R_4 together with the nitrogen atom form a morpholino, piperidino or pyrrolidino ring, and n is 1 or 2, by reacting a 1-phenyl-1-hydroxy-alkylamine of the formula



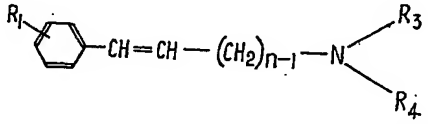
(II)

or a 1-phenyl-1-halogenoalkylamine of the formula



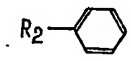
(III)

in which Hal represents a halogen atom, preferably a chlorine atom, or a 1-phenyl-1,2-unsaturated alkenylamine of the formula



(IV)

in which R_1, R_3 and R_4 and n have the meanings given above, with an aryl compound of the formula



(V)

in which R_2 has the meaning given above, in

the presence of Friedel-Crafts catalysts such for example as gallium trichloride, boron trifluoride or, preferably, aluminium trichloride.

The following phenylalkyl compounds may be used as one reactant in the process of the present invention:

1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane,
1 - *p* - methoxy - phenyl - 1 - hydroxy - 3-(1 - phenyl - propyl - (2) - amino) - propane,
1 - *m* - chlorophenyl - 1 - hydroxy - 3 - (1-phenyl - propyl - (2) - amino) - propane,
1 - *o* - tolyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1 - *m* - methoxy - phenyl - propyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-butyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (2 - phenyl-ethylamino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1- phenyl-propyl - (2) - methylamino) - propane,
1 - phenyl - 1 - hydroxy - propylamine - (3),
1 - phenyl - 1 - hydroxy - ethylamine - (2),
1 - phenyl - 1 - hydroxy - 3 - isopropyl-amino - propane,
1 - phenyl - 1 - hydroxy - 2 - morpholino-ethane, and the analogous
1 - phenyl - 1 - chloro - compounds and
1 - phenyl - 1,2 - unsaturated compounds.

As the second reactant in the process of the present invention, there may be mentioned, for example, benzene, toluene, chlorobenzene, methoxybenzene, ethoxybenzene and isopropylbenzene.

The reaction is carried out in a suitable solvent. As solvent there may be used, the second reactant in the process, which is then to be used in excess, or as an inert solvent, nitrobenzene or chlorinated hydrocarbons such as for example as carbon tetrachloride or tetrachloroethane.

The reaction is carried out at a temperature in the range of 50 and 200°C, preferably in the range of 60 and 140°C. In practice, the reaction is carried out at the boiling temperature of the solution used.

In an advantageous method for carrying out the process of the present invention, the selected 1-phenyl-1-hydroxy-alkylamine is converted with a Lewis acid, for exemple, aluminium chloride, in a suitable solvent, for example, benzene, and with the aid of an appropriate halogenating agent, preferably an acid chloride of sulphur, for example, thionyl chloride, into the corresponding chloride; the hydrochlorides of the 1-phenyl-1-chloro-compounds thus obtained are generally well crystallizable. The 1-phenyl-1-chloroalkyl-amines thus obtained are condensed at elevated temperature in one of the mentioned solvents containing the desired reactant and the Friedel-Crafts catalyst to yield the diphenyl-alkyl-amines. These two process steps may be carried out in one vessel.

According to another advantageous method of operation, the 1-phenyl-1-hydroxy-alkyl-amines can be reacted directly with the second reactant in the solvents mentioned above. The reaction may be carried out in the same way starting from the mentioned 1-phenyl-1,2-unsaturated alkylamine compounds.

As basic compounds, the products of the present invention may be converted into the corresponding salts by reacting them with inorganic or organic acids, preferably physiologically tolerable inorganic or organic acids. As inorganic acids, there may be used for example, hydrohalic acids, for example hydrochloric acid, sulphuric acid, phosphoric acid or amido-sulphonic acid. As organic acids, there may be used, for example, acetic acid, propionic acid, lactic acid, glycolic acid, gluconic acid, maleic acid, succinic acid, tartaric acid, salicyclic acid, or citric acid.

The products of the present invention may be administered parenterally or orally, as such or in the form of their salts, if desired or required in admixture with pharmaceutically usual carriers, if desired, in unit dosage form. In the case of oral application, they may be used preferably as tablets or dragees into which they, as the active substances, have been made up with the usual carriers such as lactose, starch, tragacanth and magnesium stearate.

The processes hitherto known and used for the preparation of the products of the invention are difficult and time-consuming. Some of the starting materials required for these processes are difficulty accessible. The present process makes the products more readily available as it may be carried out on the scale required for industrial use.

The following Examples illustrate the invention.

EXAMPLE 1

15.1 g of 1-phenyl-1-hydroxy-propylamine-(3) were boiled for 30 minutes with 14.5 g of phenylacetone in 50 cc of benzene and the water formed was removed by distillation with benzene. The oily residue was then taken up in 30 cc of methanol and 5 cc of water. 1.5 g of sodium boron hydride was introduced portionwise into this solution, during which time the temperature of the reaction mixture rose to 40—50°C. The reaction mixture was then heated for 30 minutes on the water bath and the solvent was removed by distillation. The oily residue was extracted with ether and alcoholic hydrochloric acid was added to the ether extract until the mixture was turbid. 25 g of 1-phenyl-1-hydroxy-3-(1-phenyl-propyl-(2)-amino)-propane-hydrochloride crystallized; the compound was found to melt at 144—146°C.

25 g of the compound thus obtained were introduced portionwise, at room temperature, into a solution of 40 cc of thionyl chloride in 80 cc of benzene. A strong evolution of hydrogen chloride and sulphur dioxide set in. After some time, the hydrochloride of 1-phenyl-1-chloro - 3 - (1 - phenyl - propyl - (2) - amino) - propane crystallized. Separation was completed by the addition of ether. 24 g of the compound which showed a melting point of 138—144°C were obtained. 10 g of this hydrochloride were suspended in 40 cc of benzene and 8 g of anhydrous aluminium chloride were added, the temperature being at about 50°C. The whole was then heated for 30 minutes under reflux. After cooling, the reaction mixture was poured in a mixture of 20 cc of concentrated hydrochloric acid, 10 cc of water and 100 g of ice. After several hours standing and after addition of ether, the hydrochloride of 1,1-diphenyl-3-(1-phenyl-propyl-(2)-amino)-propane crystallized in almost colourless crystals. The crude yield was 11.2 g; the compound was found to melt at 186—188°C (from aqueous methanol 190—192°C).

EXAMPLE 2

15 g of 1-phenyl-1-hydroxy-propylamine-(3) were introduced portionwise into a mixture of 16 cc of thionyl chloride and 30 cc of benzene. The whole was heated for 20 minutes under reflux on the water bath. After several hours standing, crystallization was completed by the addition of ether. 18.5 g of 1 - phenyl - 1 - chloro - propylamine - (3)-hydrochloride having a melting point of 110—112°C were obtained. 10 g of the hydrochloride thus obtained were suspended in 40 cc of benzene and 12 g of anhydrous aluminium chloride were added portionwise. After heating for 30 minutes on the water-bath, the reaction mixture was poured in a mixture of hydrochloric acid, water and ice. The hydrochloride of 1,1-diphenyl-propylamine-(3) melting at 206—209°C crystallized out. The yield was 12 g. After recrystallization from water, the product was found to melt at 217—218°C.

EXAMPLE 3

10 g of 1-phenyl-1-hydroxy-2-morpholino-ethane were dissolved in 30 cc of benzene. 15 g of anhydrous aluminium chloride were added portionwise in such a manner that the reaction mixture did not boil. The reaction mixture was then heated for 30 minutes on a water bath. After cooling, it was poured in a mixture of ice, water and concentrated hydrochloric acid. After some minutes, 1,1-diphenyl - 2 - morpholino - ethane - hydrochloride crystallized out. The yield was 14.6 g. After recrystallization from a mixture of isopropanol and ether, the compound was found to melt at 211—213°C.

EXAMPLE 4

8 g of anhydrous aluminium chloride were introduced in a solution of 5 g of 1-phenyl-1-hydroxy-2-benzylamino-ethane in 20 cc of toluene in such a manner that the toluene did not boil. The reaction mixture was then heated for 30 minutes to boiling temperature and after cooling it was poured into a mixture of ice, water and concentrated hydrochloric acid. 1-phenyl-1-*p*-tolyl-2-benzyl-amino-ethane-hydrochloride crystallized in a yield of 92%. By recrystallization from a mixture of isopropanol and ether, there were obtained colourless needles melting at 203—205°C.

EXAMPLE 5

12 g of styrene oxide were mixed with 13.5 g of 1-phenyl-propylamine-(2) and heated for several hours to 100—120°C. 1 - phenyl - 1 - hydroxy - 2 - (1 - phenyl-propyl - (2) - amino) - ethane was obtained in the form of an almost colourless oil. 20 g of anhydrous aluminium chloride were added portionwise to a solution of this oil in 80 cc of benzene. The mixture was heated for 30 minutes under reflux to the boiling temperature on the water bath and, after cooling, it was poured into a mixture of ice, water and hydrochloric acid. The hydrochloride of 1,1-diphenyl - 2 - (1 - phenyl - propyl - (2)-amino) - ethane separated in the form of an oil. The free base was isolated by addition of soda lye and extraction with ether. After addition of an alcoholic solution of maleic acid, the maleate, which was found to melt at 168—170°C, crystallized in a yield of 88%.

EXAMPLE 6

4 cc of water were added to a solution of 14 g of 1-phenyl-1-hydroxy-2-amino-ethane and 13.7 g of phenylacetone in 40 cc of methanol and subsequently 1.5 g of sodium boron hydride were added portionwise. After a one hour standing at room temperature, the reaction mixture was concentrated by evaporation under reduced pressure. The oily residue was taken up in 40 cc of toluene, 20 g of anhydrous aluminium chloride were added portionwise and the mixture was further treated as described in Example 5. 1 - phenyl - 1 - *p* - tolyl - 2 - (1 - phenyl-propyl - (2) - amino) - ethane in the form of a colourless oil was obtained. After addition of maleic acid, the maleate which was found to melt at 166—168°C. was obtained.

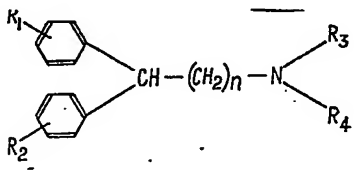
EXAMPLE 7

30 g of anhydrous aluminium chloride were added portionwise to a suspension of 29 g of 1 - phenyl - 2 - cinnamylamino - propane-hydrochloride melting at 237—240°C (prepared by condensation of cinnamic aldehyde with 1-phenyl-propyl-amine-(2) and reduction of the Schiff-base thus obtained with sodium boron hydride) in 100 cc of benzene and the reaction mixture was subsequently heated for 45 minutes to the boiling temperature. After the reaction mixture had cooled, it was

poured in a mixture of ice and hydrochloric acid as described in Example 1. After addition of ether, the crystals were separated by filtration, dissolved in methanol in order to separate mineral salts and then the compound was precipitated by the addition of water. 26.5 g of 1,1-diphenyl-3-(1-phenyl-propyl-(2)-amino)-propane-hydrochloride were obtained; the compound was found to melt at 190—192°C after recrystallization from isopropanol.

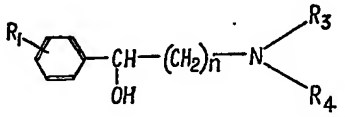
WHAT WE CLAIM IS:—

1. A process for the manufacture of diphenylalkylamines of the formula



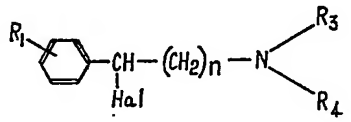
(I)

in which R_1 and R_2, which may be identical or different, represent hydrogen, an alkyl group having 1—3 carbon atoms, an alkoxy group having 1—3 carbon atoms, or halogen, R_3 represents hydrogen or an alkyl group having 1—3 carbon atoms, and R_4 represents hydrogen, an alkyl group having 1—4 carbon atoms, an aralkyl group having up to 4 carbon atoms in the alkylene chain which may be substituted in the phenyl nucleus by alkyl or alkoxy groups having 1—3 carbon atoms, or in which R_3 and R_4 together with the nitrogen atom form a morpholino, piperidino or pyrrolidino ring, and n represents 1 or 2, wherein a 1-phenyl-1-hydroxy-alkylamine of the formula



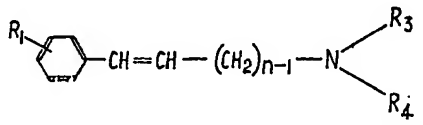
(II)

or a 1-phenyl-1-halogenoalkylamine of the formula



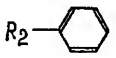
(III)

in which Hal represents a halogen atom, or a 1-phenyl-1,2-unsaturated alkenylamine of the formula



(IV)

in which R_1, R_3 and R_4 and n have the meaning given above, is reacted with an aryl compound of the formula

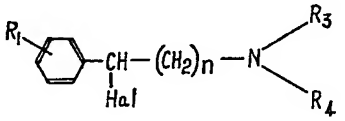


(V)

in which R_2 has the meaning given above, in the presence of Friedel-Crafts catalysts.

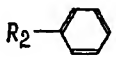
2. A process as claimed in claim 1, in which R_1 or R_2 represents or both R_1 and R_2 represent chlorine.

3. A process as claimed in claim 1 or claim 2, in which a 1-phenyl-1-chloroalkylamine of the formula



(III)

in which R_1, R_2, R_4, and n have the meanings given in claim 1 and Hal represents chlorine is reacted with an aryl compound of the formula



(V)

in which R has the meaning given in claim 1, in the presence of Friedel-Crafts catalysts.

4. A process as claimed in any one of claims 1 to 3, wherein the Friedel-Crafts catalyst is aluminium trichloride.

5. A process as claimed in any one of claims 1 to 4, wherein the Friedel-Crafts catalyst is gallium trichloride or boron trifluoride.

6. A process as claimed in claim 1, wherein 1-phenyl-1-hydroxy-3-(1-phenyl-propyl-(2)-amino)-propane is used as a reactant.

7. A process as claimed in claim 1, wherein 1 - *p* - methoxy - phenyl - 1 - hydroxy-3 - (1 - phenyl - propyl - (2) - amino) - propane is used as a reactant.

8. A process as claimed in claim 1, wherein 1 - *m* - chloro - phenyl - 1 - hydroxy - 3 - (1-

phenyl - propyl - (2) - amino) - propane is used as a reactant.

9. A process as claimed in claim 1, wherein 1 - *o* - tolyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane is used as a reactant.

10. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1 - *m*-methoxy - phenyl - propyl - (2) - amino)-propane is used as a reactant.

11. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-butyl - (2) - amino) - propane is used as a reactant.

12. A process as claimed in claim 1, wherein 1 - phenyl - 1- hydroxy - 3 - (2 - phenyl-ethylamino) - propane is used as a reactant.

13. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1-phenyl - propyl - (2) - methylamino) - propane is used as a reactant.

14. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - propylamine-(3), is used as a reactant.

15. process as claimed in claim 1, wherein 1 - phenyl - hydroxy - ethylamine-(2), is used as a reactant.

16. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - isopropyl-amino - propane, is used as a reactant.

17. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 2 - morpholino-ethane, is used as a reactant.

18. A process as claimed in any one of claims 6 to 17, wherein instead of the 1-phenyl-1-hydroxy alkylamine there is used the corresponding 1-phenyl-1-chloroalkylamine.

19. A process as claimed in any one of claims 6 to 17, wherein instead of the 1-phenyl-1-hydroxyalkylamine there is used the corresponding 1-phenyl-alken-1,2-ylamine.

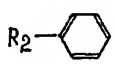
20. A process as claimed in any one of claims 1 to 19, wherein benzene, toluene, chlorobenzene, methoxybenzene, ethoxy-benzene, or isopropylbenzene is used as second reactant.

21. A process as claimed in any one of claims 1 to 20, carried out at a temperature within the range of 50 to 200°C.

22. A process as claimed in claim 21, carried out at a temperature within the range of 60 to 140°C.

23. A process as claimed in any one of claims 1 to 22, carried out in an inert solvent.

24. A process as claimed in any one of claims 1 to 23, wherein an excess of the reaction component of the formula



where R_2 has the meaning given in claim 1, is used as a solvent.

25. A process as claimed in claim 23 or claim 24, carried out at the boiling temperature of the solution used.

26. A process as claimed in claim 1 carried out substantially as described in any one of the Examples herein.

27. Diphenylalkylamines whenever prepared by the process claimed in any one of claims 1 to 26.

28. 1,1 - diphenyl - 3 - (1 - phenyl-propyl - (2) - amino)propane whenever prepared by a process as claimed in claim 1.

29. 1,1 - diphenyl - propylamine - (3) whenever prepared by a process as claimed in claim 1.

30. 1,1 - diphenyl - 2 - morpholino ethane whenever prepared by a process as claimed in claim 1.

31. 1 - phenyl - 1 - *p* - tolyl - 2 - benzyl-aminoethane whenever prepared by a process as claimed in claim 1.

32. 1,1 - diphenyl - 2 - (1 - phenyl-propyl - (2) - amino)ethane whenever prepared by a process as claimed in claim 1.

33. 1 - phenyl - 1 - *p* - tolyl - 2 - (1-phenyl - propyl - (2) - amino - ethane whenever prepared by a process as claimed in claim 1.

34. 1,1 - diphenyl - 3 - (1 - phenyl-propyl - (2) - amino)propane whenever prepared by a process as claimed in claim 1.

35. A salt of a diphenylalkylamine claimed in any one of claims 27 to 34, the diphenyl-alkylamine having been prepared by a process as claimed in claim 1.

36. A physiologically tolerable salt of a diphenylalkylamine claimed in any one of claims 27 to 34, the diphenylalkylamine having been prepared by a process as claimed in claim 1.

37. Pharmaceutical preparations containing a diphenylalkylamine as claimed in any one of claims 27 to 34 in admixture or conjunction with a pharmaceutically acceptable excipient.

38. Pharmaceutical preparations containing a physiologically tolerable salt of a diphenyl-alkylamine as claimed in claim 36, in admixture or conjunction with a pharmaceutically acceptable excipient.

39. Pharmaceutical preparations as claimed in claim 37 or claim 38 in unit dosage form.

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